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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/060,301	02/01/2002	Yusuke Nakamura	1254-0195P	7091

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EXAMINER	
KIM, YOUNG J	
ART UNIT	**PAPER NUMBER**
1637	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/060,301	NAKAMURA ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on November 9, 2007 has been entered.

Preliminary Remark

Claim 4 is canceled.

Claims 9 and 10 are new.

Claims 1-3 and 5-10 are pending and are under prosecution herein.

Claim Rejections - 35 USC § 112

The new matter rejection of claims 1-3 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, made in the Office Action mailed on October 13, 2006 is withdrawn in view of reconsideration of the application.

Rejection, Maintained

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The new matter rejection of claims 5-8 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, made in the Office Action mailed on October 13, 2006 is maintained for the reasons of record.

Claim 5 has been amended to recite that the method simultaneously amplifies ***up to 400*** of nucleotide sequences using 10-40 ng of starting genomic DNA, said assay allowing the detection of at least 98% of SNPs.

This translates to 0.025-0.1 ng starting DNA.

The specification simply does not have any justification for this range.

Applicant's arguments do not address this aspect of the new matter.

Claim Rejections - 35 USC § 103 - Maintained

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1, 3, 5, and 7 under 35 U.S.C. 103(a) as being unpatentable over Mein et al. (Genome Research, March 2000, vol. 10, no. 3, pages 330-343) in view of Wang et al. (Science, May 1998, vol. 280, pages 1077-1082), made in the Office Action mailed on October 13, 2006 is maintained for the reasons of record.

In addition, claims 9 and 10 are rejected herein as being necessitated by Amendment.

Applicants' arguments presented in the Amendment received on October 31, 2007 have been fully considered but they are not found persuasive for the reasons set forth in the, "Response to Arguments," section.

The Rejection:

Preliminarily, the full-breadth of the claims are construed as follows.

The limitation imposed by the phrase, "genomic DNA whose amount is 10-40 ng per 100 sites," embodies a range of 0.1 ng to 0.4 ng per a single SNP site. Thus, the method requires at least 0.2 ng of genomic DNA in claims 1 and 3 which recite the step of simultaneously amplifying "at least two sites," and at least 0.1 ng of genomic DNA in claims 5-8 which recite the step of simultaneously amplifying one or more sites."

Additionally, claims 7 and 8 does not require that the 50 pairs of more primer be primer pairs which amplifies different SNP sites. Thus, employing at least 50 pairs of the primer pairs which amplify a single SNP site (i.e., having the same sequences) would necessary meet this limitation.

While Applicants' arguments are moot in view of this new ground of rejection, to the extent applicable, the arguments will be addressed in the, "Response to Arguments" section.

Mein et al. disclose a method of coupling multiplex amplification of polymorphic loci from a genomic DNA, followed by detecting the single nucleotide polymorphisms by Invader® assay method (Abstract, page 331, 2nd column).

Mein et al. disclose that 36 SNPs sites were amplified (page 331, 2nd column), employing 10 ng of starting DNA. Mein et al. are silent as to how many SNP sites were simultaneously amplified using the 10 ng of starting DNA.

Hence, Mein et al. do not employ 50 or more primer pairs in their method nor genomic DNA whose amount is 10-40 ng per 100 sites.

Wang et al. disclose a method of detecting SNPs by first simultaneoutly amplifying (or multiplexing) a plurality of primer pairs, including 558 loci, necessarily including more than 50 primer sets, considering that a singe primer set amplifies a single loci (page 1080, 3rd column).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Mein et al. with the teachings Wang et al. to arrived at the claimed invention for the following reasons.

The motivation to multiplex more target sites in amplification, that is, simultaneously amplifying multiple target sites, is a well-established desire in the art. As Wang et al. put it:

> "We next sought to **decrease substantially the sample preparation required to generate large numbers of SNPs, as required to perform a genome scan. We developed a protocol based on multiplex PCR in which primer pairs from many different loci are combined in a single reaction**." (page 1080, 3rd paragraph, 1st paragraph)

Wang et al. employ 100 ng of DNA for simultaneously amplifying a plurality of loci, including 24 sets of approximately 23 loci, 12 sets of approximately 46 loci, 6 sets of approximately 92 loci (page 1080, 3rd paragraph, 1st paragraph), and a single set of 558 loci.

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings of Mein et al. with the teachings of Wang et al. to arrive at simultaneously amplification involving at least 50 pairs of primers or more.

Wang et al. disclose that 12 sets of 46 loci; (46 loci being amplified simultaneously); 6 sets of 92 loci; a single set of 558 loci were amplified simultaneously (page 1080, 3rd column).

While the artisans disclose that different multiplex amplification reactions gave different percentage of loci being successfully amplified, Wang et al. explicitly discusses that it may be possible to salvage the unsuccessful assays by grouping them into additional multiplex sets or by *redesigning* the assays.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings of Mein et al. and the teachings of Wang et al. to achieve multiplex amplification involving a plurality of primers for the advantage of decreasing sample preparation (as expressed by Wang et al.), wherein the artisan would have had a reasonable expectation of success at such combination as Wang et al. clearly envisions that by redesigning, multiplexing even up to 558 loci would be achievable, through optimization.

Regarding optimization, the MPEP 2144.05(II)(A) clear that, "differences in concentrations or temperature ***will not support*** patentability of subject matter encompassed by prior art unless there is evidence indicating such concentration or temperature is critical," citing *In re Aller,* F.2d 454, 456, 105 USPQ 233, 235, (CCPA 1995). Analogously, optimizing parameters for multiplexing multiple target sites in an amplification reaction would be considered routine, as provided for by Wang et al.

In addition, based on the fact that a single multiplex amplification involving 100 ng of DNA for amplifying 558 loci resulted in a 50% success, one of ordinary skill in the art would have had a reasonable expectation of success at employing half the number of the loci (approximately 279 loci), with the 100 ng of starting DNA (which would result in 0.36 ng per target site) with close to a 100% success.

Therefore the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments:

Applicants state that the *prima facie* case has not been demonstrated because the combination of the teachings do not result in at least 98% successful detection have not been achieved by the artisans, but only 50% successful detection of the sites (page 6, bottom paragraph, Response).

Applicants state that the supposition made at the 3rd paragraph of page 10 in the previous Office Action is incorrect (page 7, 1st paragraph, Response).

This argument is not found persuasive for the following reasons.

The statement made in the above-referred to section is as follows:

"In addition, based on the fact that a single multiplex amplification involving 100 ng of DNA for amplifying 558 loci resulted in 50% success, one of ordinary skill in the art would have had a reasonable expectation of success at employing half the number of the loci (approximately 279 loci) with the 100 ng of starting DNA (which would result in 0.36 ng per target site) with close to a 100% success."

Wang et al. were able to employ 100 ng of starting DNA to successfully amplify half of 558 loci, which translates to about 279 loci.

So, if one were to employ 100 ng of the starting DNA to amplify those loci which were successfully amplified previously, why would one expect the amplification to not work?

As previously stated, 100 ng of starting DNA for amplifying 279 loci calculates to about 0.36 ng, which is clearly within Applicants' claims.

Applicants state that they had previously explained that the rate of successful typing is not a linear function of the **input DNA amount or the number of loci amplified at once**, but rather, failure of the typing assays occur at least partly due to primer dimer formation and annealing of primers to secondary (i.e., not the target locus) sites in the genome (page 7, 3rd paragraph, Response).

Applicants are respectfully requested to be consistent in their arguments and the position taken.

Applicants previously stated because Applicants were capable of typing 0.1 ng of DNA for a ***single site***, one could multiplex 100 sites using only 10 ng of starting DNA (see page 5, bottom paragraph, Response).

If the rate of successful typing is not a linear function of the input DNA amount of the number of loci amplified at once, then how are Applicants asserting that because 0.1 ng of DNA can be used for amplifying a single site, 100 sites can be ***multiplexed*** with only 10 ng (0.1 x 100) starting DNA?

Applicants also even have drawn to typing 400 sites using 0.1 ng to 0.4 ng of DNA per site, with additional claims which do not even limit the total number of targets which can be amplified simultaneously (claims 9 and 10), which embraces simultaneously amplifying 1,000, 10,000, 100,000, or more sites using 0.1 to 0.4 ng of DNA per site, solely based on Applicants' discovery that a single site can be typed (not a multiplex) based on 1 ng of starting DNA, all of which can be done with 98% success rate. Has Applicants not taken in to account the formation of primer-dimers and annealing of primers to secondary (i.e., not the target locus) sites in the genome?

The position taken by the Office is more reasonable than that which is taken by Applicants. That is to say, if Wang et al. was able to successfully amplify 50% of 558 loci (279 loci), which would necessarily require successful amplification of at least half of 558 loci, involving 100 ng of starting DNA, why would one not expect that employing those successful loci using 100 ng of starting DNA would result in at least 98% detection?

Lastly, Applicants refer to the Declaration of Dr. Nakamura in their response (page 7, bottom paragraph), but said declaration is unsigned and no signed copy has been received. And

even if, *arguendo,* the Declaration were to be submitted properly, the Declaration can only demonstrate unexpected result, that is, amplifying 100 loci using 40ng of DNA, with 98% proficiency, and not for the entire breadth of the claims.

Applicants' arguments are not persuasive, and the rejection is maintained therefore.

The rejection of claims 2, 6, and 8 under 35 U.S.C. 103(a) as being unpatentable over Mein et al. (Genome Research, March 2000, vol. 10, no. 3, pages 330-343) in view of Wang et al. (Science, May 1998, vol. 280, pages 1077-1082) as applied to claims 1, 3, 5, 7, 9, and 10 above, and further in view of Brooks (US 2001/0046670 A1, issued November 29, 2001, priority October 7, 1999), made in the Office Action mailed on October 13, 2006 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on October 31, 2007 have been fully considered but they are not found persuasive for the reasons already discussed above.

The Rejection:

The teachings of Mein et al. and Wang et al. have already been discussed above.

Neither Mein et al. nor Wang et al. employ "hot start" amplification (claims 2, 6, and 8)

Brook discloses a multiplex amplification [0076] reaction which involves hot start amplification [0066].

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Mein et al., and Wang et al. with the advantage offered by Brooks to arrive at the invention as claimed for the following reasons.

Brook clearly discusses the advantage of employing "hot start" PCR method:

"...other 'Hot Start' type PCR conditions are used to limit primer dimer artifacts as much as possible." [0066].

As one of ordinary skill in the art in the art of amplification would recognize that primer dimer artifacts are to be minimized in amplification procedures, it would have been obvious to implement this teachings into the teachings of Mein et al., and Wang et al. to arrive at the claimed invention with a reasonable expectation of success.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m (M-W and F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent

to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Young J. Kim
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Art Unit 1637
1/10/2008

YOUNG J. KIM
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